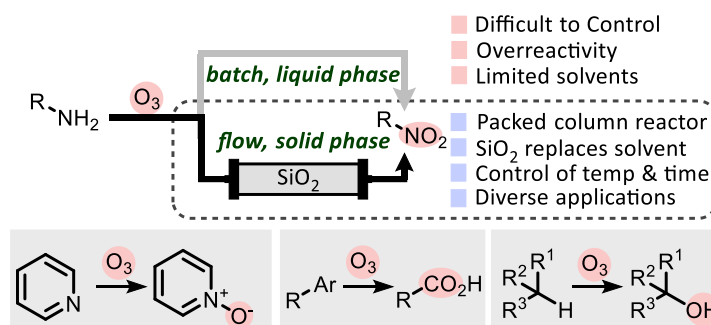


# Ozone-Mediated Amine Oxidation and Beyond: A Solvent Free, Flow-Chemistry Approach

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**ABSTRACT:** Ozone is a powerful oxidant, most commonly used for oxidation of alkenes to carbonyls. The synthetic utility of other ozone-mediated reactions is hindered by its high reactivity and propensity to over-oxidize organic molecules, including most solvents. This challenge can largely be mitigated by adsorbing both substrate and ozone onto silica gel, providing a solvent-free oxidation method. In this manuscript, a flow-based packed bed reactor approach is described that provides exceptional control of reaction temperature and time of this reaction to achieve improved control and chemoselectivity over this challenging reaction. A powerful method to oxidize primary amines into nitroalkanes is achieved. Examples of pyridine, C–H bond, and arene oxidations are also demonstrated, confirming the system is generalizable to diverse ozone-mediated processes.

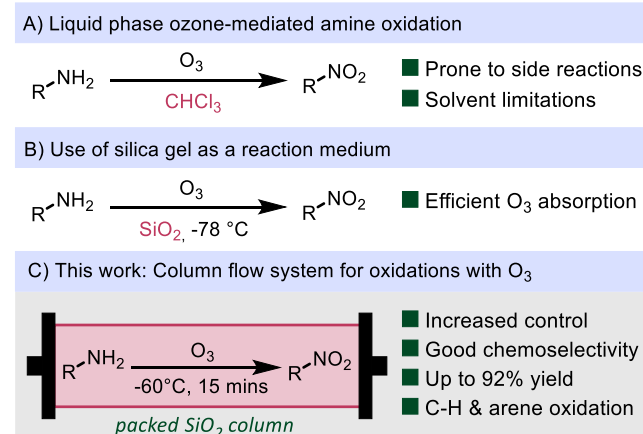


## □ Introduction

Ozone is an extremely powerful oxidizing agent, capable of reacting with a wide array of organic and inorganic compounds. This high reactivity allows ozone to act as a powerful disinfectant, and combined with UV irradiation, is a common and effective method to sterilize drinking water. In organic synthesis, this ability of ozone to exhaustively oxidize a broad range of functional groups leads to challenges in chemoselectivity. The most often used application comes from the oxidation of alkenes.<sup>1</sup> The popularity of this reaction spawned further investigations into ozone's synthetic usefulness, but no other developed method has thus far enjoyed the wide applicability that was afforded to alkene ozonolysis. While many other functional groups can be oxidized by ozone, these reactions are slower and are thus more susceptible to chemoselectivity issues. In other words, the lack of control over ozone's extreme reactivity often results in substrate overoxidation and degradation. This is unfortunate, since ozone is among the most atom economical oxidizing agents, usually prepared from molecular oxygen and producing O<sub>2</sub> as the only waste product.

While not nearly as popular or thoroughly explored as ozonolysis, other synthetic applications of ozone have been discovered and used. For instance, tertiary C–H bond hydroxylation,<sup>2</sup> synthesis of N-oxides from pyridines,<sup>3</sup> and the transformation of arenes into carboxylic acids<sup>4</sup> have been described. One particularly interesting application of ozone is in the reaction with amines. While it was previously thought that ozone degrades primary amines,<sup>5,6</sup> later evidence demonstrated that carefully chosen conditions could give detectable quantities of nitroalkane products.<sup>7</sup> These substrates can act as versatile intermediates for further derivatization, and can be readily converted into

## Scheme 1: Evolution of amine ozonation strategies over time



most other functional groups in a handful of steps.<sup>8</sup> Existing means of performing this amine oxidation most commonly involve hazardous reagents such as hypofluorous acid<sup>9</sup> or Caro's acid,<sup>10</sup> both of which present a serious threat of explosion and injury if mishandled in a lab setting. Less hazardous reagents for amine oxidation include organic peroxides such as m-CPBA<sup>11</sup> or dimethyldioxirane.<sup>12</sup> Less reactive hydrogen peroxide can be coerced to perform this transformation as well, but this usually requires metal catalysts such as tungsten or rhenium.<sup>13–15</sup> Ozone-mediated amine oxidation has the potential to be an appealing alternative to these methods, yet.

Initial reports on ozone-mediated amine oxidation in organic solvents note moderate yields and formation of a wide range of

byproducts resulting from side chain oxidation or decomposition via radical or carbocation intermediates (**Scheme 1a**).<sup>7,16–18</sup> Furthermore, the authors found that solvent selection played a key role in byproduct distribution and selectivity of the reaction. Halogenated solvents such as chloroform gave the best yields and product selectivity, but also formed phosgene gas when degraded by ozone. Less hazardous solvent choices such as methanol or pentane reacted more with ozone and gave a wider range of byproducts and lower yields.

Towards overcoming issues associated with solvent degradation in challenging ozone-mediated oxidations, Mazur *et al.* developed a strategy to adsorb substrates onto silica gel to act as a solid matrix (**Scheme 1b**).<sup>19</sup> In many ways, silica is an ideal solvent-replacement: it is inexpensive, reusable, inert to ozone, and is able to adsorb ozone more efficiently than most organic solvents, particularly at cryogenic temperatures.<sup>20,21</sup> With this approach, oxidation of C–H bonds to form alcohols or ketones<sup>22</sup> and oxidation of amines to nitroalkanes were reported with improved yields and selectivity compared to use of organic solvents.<sup>19</sup> While this represented a substantial improvement over previously reported liquid-phase oxidations, there are still many limitations that have kept this chemistry from being used. One such limitation lies in the lack of fine control over the reaction conditions in this solid/gas biphasic reaction. Given the aggressive nature of ozone, dialing in a specific contact time at a specific temperature is important but challenging in the batch system. For example, the described procedure involves blowing ozone gas over the cryogenically cooled silica gel for a set amount of time, then holding for another set of time before warming to room temperature.

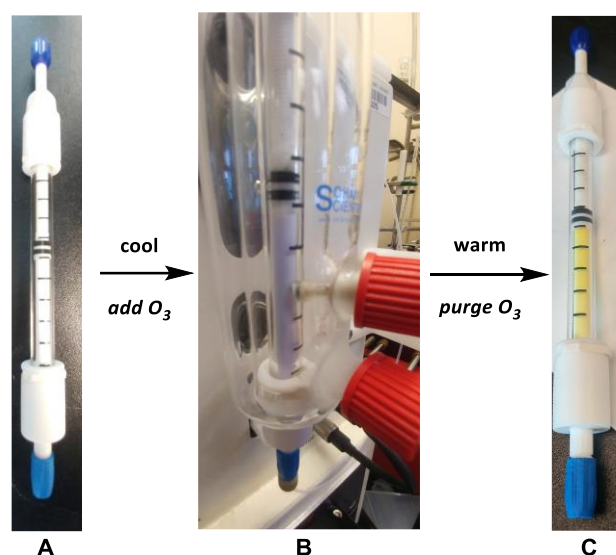
We hypothesized that the inherent lack of control in this batch oxidation procedure is responsible for the narrow scope and lack of broader use of this method. Furthermore, the reaction can be challenging to scale in a controlled manner, since the amount of time required to saturate the silica gel with ozone will increase in large-scale reactions, increasing the risk of substrate degradation by overoxidation. Flow chemistry is a well-established technology for improving reproducibility, enhancing mass/heat transfer, and providing finer control over process parameters compared to batch. In addition, it has been previously established that ozone-mediated reactions can be scaled up in flow while still minimizing associated safety risks.<sup>23</sup> For these reasons, we proposed that a flow system would be ideal for performing underutilized ozone-mediated oxidation reactions. While several powerful oxidation procedures have been developed since this field's inception, ozone remains an appealing inexpensive and atom economical oxidant. Herein, we present a flow reactor platform designed to harness the synthetic power of ozone and tempering it with fine levels of control to perform a series of challenging oxidations (**Scheme 1c**). A focus is made on the oxidation of amines to nitroalkanes, with examples of pyridine, C–H bond, and arene oxidation demonstrating that the system is general and capable of a range of transformations.

## □ Results and Discussion

We set out to design a reactor to gain control over the behavior and reactivity of ozone. In the batch system, silica gel and adsorbed substrate are chilled to cryogenic temperatures, saturated with O<sub>3</sub>, and allow to age for an appropriate amount of time before stopping the O<sub>3</sub> stream and warming to room temperature. We proposed that a packed column reactor would allow more precise control. Controlling temperature, saturating

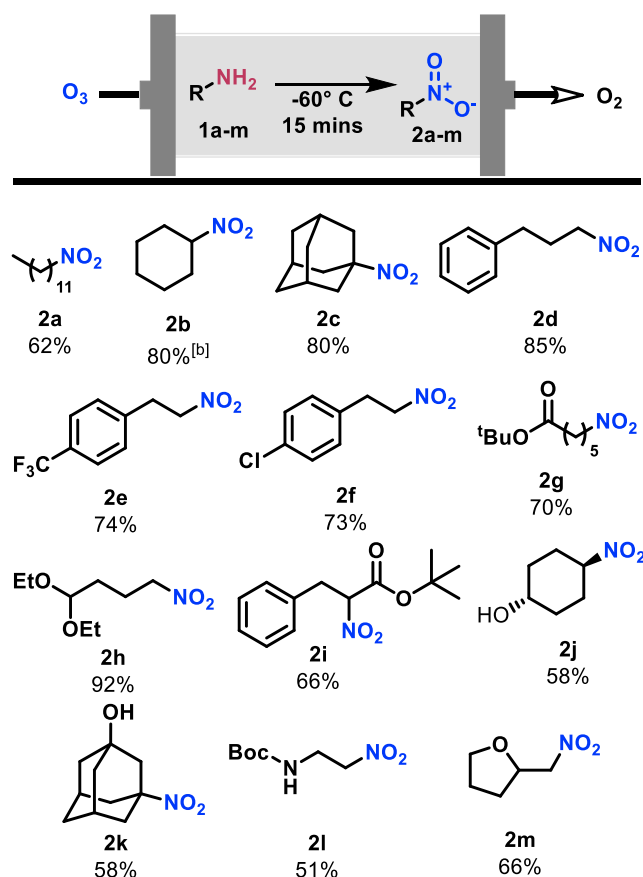
the system with O<sub>3</sub>, and terminating the reaction by flushing with O<sub>2</sub> may be achieved more efficiently due to the compact size of the system and the improved contact between the gas and solid phases in the column relative to a flask. Given the high reactivity of ozone and the propensity of organic molecules to undergo overoxidation, this added aspect of control and precision could lead to improved chemoselectivity and functional group tolerance.

In our reactor design, reactant is adsorbed onto silica gel and packed into a column (**Figure 1a**). The column is connected to a Vapourtec cooling module, chilled, and exposed to a stream of ozone. After around 15 seconds, the silica gel gains a blue tinge, indicative of saturation (**Figure 1b**). After the desired reaction time, the ozone generator is turned off so that only oxygen flows through the column. The blue colour fades within 5 seconds, leaving the newly formed product (often yellow in color) behind on the silica gel (**Figure 1c**). The reactor is allowed to warm to room temperature before the silica gel is collected and the product is extracted from the surface.



**Figure 1:** a) Immobilized amine before reaction. b) Reaction in progress with adsorbed ozone. c) Product adsorbed onto silica gel after reaction completion.

For the oxidation of amines, optimal reaction conditions were identified with a reaction temperature of -60 °C and a reaction time of 15 minutes. Longer reaction times resulted in decomposition of the product, while shorter times resulted in large amounts of recovered starting material, highlighting the sensitivity of the reaction to over- and under-oxidation (**Table S1**). With these optimized conditions, the scope of the reaction of ozone with various silica-suspended amines was investigated (**Error! Reference source not found.**). Amines situated on primary, secondary, and tertiary alkyl chains were effectively converted to nitroalkanes in moderate to good yields (**2a-c**). Amines bearing electron-neutral and electron-deficient aromatic rings were cleanly oxidized with no evidence of ring oxidation (**2d-f**). When electron rich aromatic rings were attempted no product was detected, likely due to ring oxidation and degradation. Esters and acetal groups were both tolerated admirably under the reaction conditions and products could be isolated in good to excellent yields (**2g-i**).

Scheme 2: Amine to Nitro Ozonation Scope<sup>a</sup>

<sup>[a]</sup> Reactions performed on a 0.1 mmol scale. Yields calculated as an average over two runs.

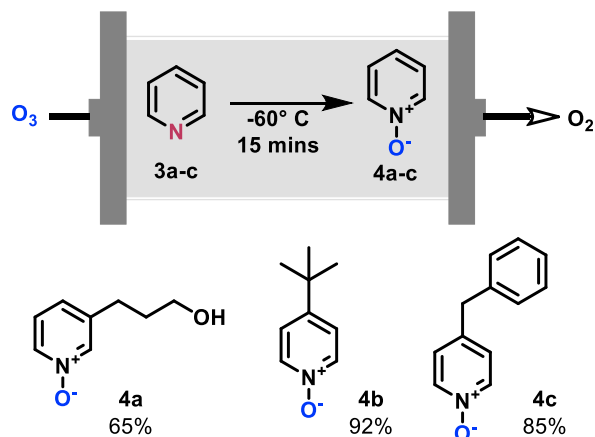
<sup>[b]</sup> Yield determined by <sup>1</sup>H NMR due to volatility of the product.

Secondary and tertiary alcohols were also tolerated (**2j** and **2k**) despite alcohol oxidation being another prominent reaction that ozone can mediate.<sup>24</sup> Trans-4-hydroxycyclohexylamine (**1j**) was found to give the corresponding trans product **2j** stereospecifically. Finally, protected amines and a tetrahydrofuran ring were also tolerated, giving modest yields of oxidation products **2l** and **2m**. Due to multiple equivalents of ozone being used in this system, selectivity between multiple amines cannot be achieved with our current flow rate and ozone concentration.

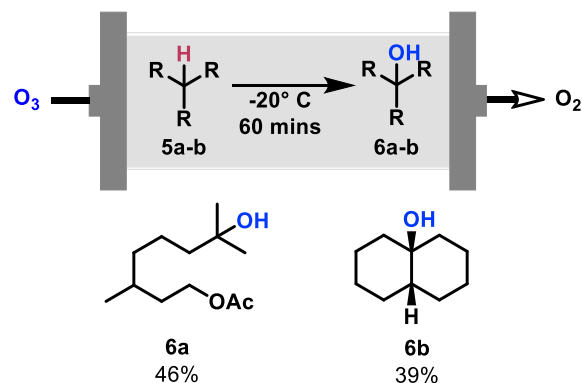
With this amine oxidation method showing tolerance for arenes, esters, alcohols, ethers, and carbamates, we were curious if other classes of ozone-mediated oxidation could be achieved using this reactor design. Pyridine *N*-oxides are valuable molecules, often formed by the treatment of the corresponding pyridine with *m*-CPBA.<sup>25</sup> Without reoptimization, our conditions could smoothly oxidize pyridines bearing alcohol (**4a**), tert-butyl (**4b**), and oxidizable benzylic C–H bonds (**4c**) to form the corresponding *N*-oxides in 65–92% yield (Scheme 3a). We next investigated applications to hydroxylation of tertiary C–H bonds.<sup>2,22</sup> This important class of reactions is often achieved by a mixture of nitric and sulfuric acid,<sup>26</sup> or a variety of transition metal catalysts,<sup>27,28</sup> leaving room for improvement for more atom economical methods. Given the resistance to the C–H bonds present in the substrates and products discussed thus far, more aggressive conditions are needed for this transformation. We found that a reaction temperature of  $-20^\circ\text{C}$  and a 1 h reaction time allowed for the formation of oxidized species **6a**

Scheme 3: Additional Oxidations Scope<sup>a</sup>

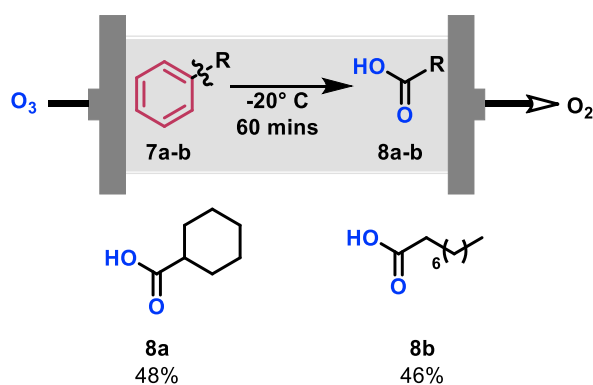
## A) Ozone-Mediated Pyridine Oxidation



## B) Ozone-Mediated C–H Hydroxylation



## C) Ozone-Mediated Arene Oxidation



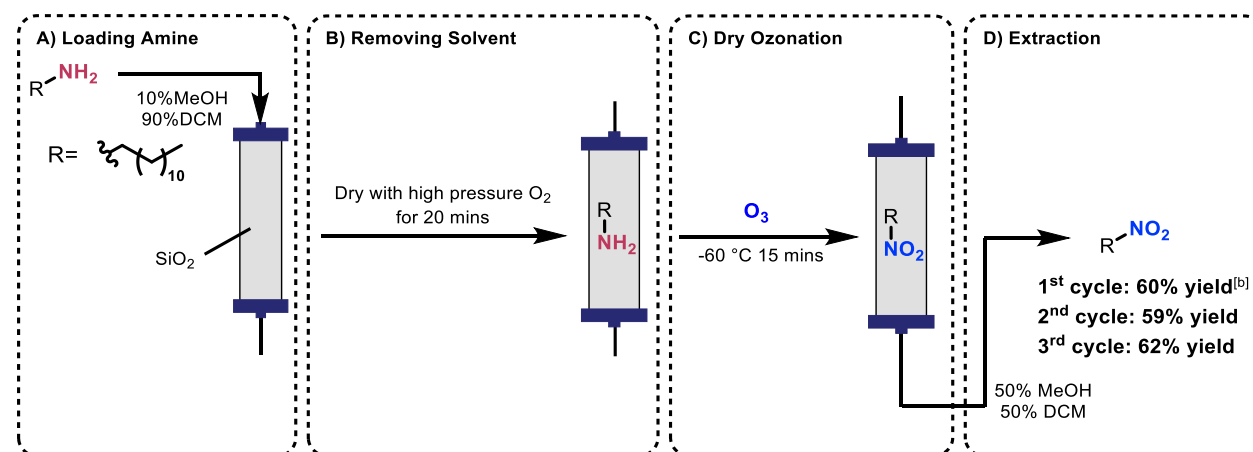
<sup>[a]</sup> Reactions performed on a 0.1 mmol scale. Yields calculated as an average over two runs.

in 46% yield, and **6b** formed stereospecifically from cis-decalin in 39% yield (Scheme 3b). Notably, both of these substrates bear two tertiary C–H bonds. The acetate group of **6a** presumably deactivates the nearest methine, and the electronegative oxygen atom in alcohol **6b** causes the product to be less reactive than the starting material. Lastly, the oxidation of aromatic rings was investigated, which is a powerful but seldom used method to prepare carboxylic acids.<sup>4,29</sup> Arenes were left untouched in with the low temperature and short reaction times described for

amine oxidation, indicating more aggressive conditions would be needed again. Using the same conditions for C–H bond hydroxylation enabled direct conversion of phenyl substituents into aliphatic acids in modest yields (**Scheme 3c**~~Error! Reference source not found.~~). While these various transformations were not subjected to rigorous optimization, the diversity of oxidations that this packed bed reactor can facilitate highlights the promise of ozone's synthetic use beyond classical ozonolysis.

Due to the small size of the Vapourtec cooled column reactor platform used for this chemistry, the system is not immediately applicable to larger scale synthesis without acquiring different equipment. However, the short reaction times employed and the use of silica gel as the solid support allows the chemistry to be automatically repeated in series to acquire larger quantities of material. With this alternative setup for amine oxidation, the substrate is dissolved in a 10% solution of methanol in DCM

#### Scheme 4: Reactor Cycling<sup>a</sup>



<sup>[a]</sup> All reactions were performed on a 0.1 mmol scale.

<sup>[b]</sup> % Yield determined by <sup>1</sup>H NMR using 1,3,5-trimethoxybenzene as an internal standard.

## Conclusion

Ozone is a powerful oxidant but is seldom used in organic synthesis for reactions other than classical ozonolysis. Due to its ability to oxidize amines, pyridines, C–H bonds, arenes, and more, ozone-mediated reactions need to be performed carefully with conditions tuned to achieve the specific sought after transformation. By using a column packed with substrate immobilized onto silica gel, our oxidation platform is capable of harnessing the high reactivity of ozone for productive chemistry. The synthesis of nitroalkanes from alkylamines is highlighted, along with select examples of pyridine N-oxide, alcohol, and carboxylic acid synthesis, highlighting the versatility of this system. While the platform described is limited in scale due to the size of the equipment used, the reactor can be iteratively cycled to achieve modest throughput and may be amenable to automation to access synthetically useful quantities of material.

## ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

## AUTHOR INFORMATION

which can be loaded onto the column (**Scheme 4a**). After the amine has been loaded, a stream of O<sub>2</sub> is passed over the column to remove the solvents that may interfere with subsequent oxidations (**Scheme 4b**). At this stage, the process occurs as previously outlined, with cooling to -60 °C, passing ozone over the silica gel for 15 minutes, sparging with O<sub>2</sub>, and warming to room temperature (**Scheme 4c**). A solution of 50% MeOH and DCM is then pushed through the column to extract the product (**Scheme 4d**). This process can then be immediately repeated with no impact on yield, allowing the procedure to be done in cycles to provide synthetically useful quantities of product (See Supporting Information Table S2).

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## Notes

Any additional relevant notes should be placed here.

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